b) the antisense oligonucleotide comprises a maximum of twelve elements, the twelve elements being capable of forming three hydrogen bonds each to cytosine bases,

c) the antisense oligonucleotide does not contain four or more consecutive elements capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target nucleic acid sequence,

d) the antisense oligonucleotide does not contain two or more series of three consecutive elements capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target nucleic acid sequence, and

e) the ratio of residues forming two hydrogen bonds each with the target nucleic acid sequence with respect to residues forming three hydrogen bonds each with the target nucleic acid sequence is

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R} + \text{2H-bond-R}} \geq 0.29$$

wherein

- 3H-bond-R = residues forming three hydrogen bonds per residue and
- 2H-bond-R = residues forming two hydrogen bonds per residue,

– generating the designed antisense oligonucleotide, and

– synthesizing the generated antisense oligonucleotide.

71. The method according to claim 70, wherein the four or more consecutive elements not contained in the antisense oligonucleotide are each guanosine.

72. The method according to claim 70, wherein the three consecutive elements in the two or more series not contained in the antisense oligonucleotide are each guanosine.

73. The method according to claim 70, wherein the generated oligonucleotide complies with the following specification

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R + 2H-bond-R}} = 0.33 \text{ to } 0.86.$$

74. The method according to claim 70, wherein the generated oligonucleotides are modified for higher nuclease resistance than naturally occurring oligo- or polynucleotides.

75. The method according to claim 74, wherein the generated oligonucleotides are modified at the bases, the sugars or the linkages of the oligonucleotides, preferably by phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases.

76. The method according to claim 75, wherein the oligonucleotide has at least two different types of modifications.

77. The method according to claim 70, wherein the oligonucleotides are reacted with folic acid, hormones such as steroid hormones or corticosteroids or derivatives thereof by linking the oligonucleotides covalently to or mixing with folic acid, hormones such as steroid hormones or corticosteroids, peptides, proteoglycans, glycolipids or phospholipids.

78. An antisense oligonucleotide or derivative thereof obtainable according to the method according to claim 70 except oligonucleotides represented by SEQ ID NOS: 826-1272.

REMARKS

The specification is amended, hereby, to indicate that the instant application represents the national stage of an international application under the PCT, as required in accordance with PTO Rules.

Claims 70-78, presented hereby in place of claims 52-58, are pending. Claims 59-69 stand withdrawn from consideration pursuant to restriction under 35 USC 121.

The subject matter of claim 52 is represented by claims 70, 71, and 72, presented hereby, rewritten in order to more clearly define the subject invention. Claim 70 corresponds to claim 52